REMARKS

By the present amendment, Applicants have amended the specification to refer to SEQ ID NOS, and have amended Claim 275. Claim 275 was presented with Applicants' Preliminary Amendment dated August 6, 2004, which is a substantial copy of pending Claim 6 of Short U.S. Patent No. 6,605,449 ("the '449 patent"). The '449 patent issued on August 12, 2003, and as such, Applicants have complied with 35 U.S.C. §135(b)(1).

By the present Amendment, Claim 275 is amended to replace "each chimerized but defined polynucleotide sequences encoding full-length enzymes" to "each chimerized but defined polynucleotide sequence encoding full-length enzymes". Claim 275 is also amended to respond to the rejections under 35 USC §112, second paragraph. Specifically, step (a) is modified to clarify that it is the substrate nucleic acids which encode full-length enzymes, and to clarify and to correct antecedent basis for "the aligned substrate nucleic acid sequences" by reciting that the borders are selected "by aligning" the substrate nucleic acid sequences. Applicants also note that this exact rejected language is used in Claim 6 of the Short '449 patent from which Claim 275 was copied, and as such, applies equally to that claim, and is an artifact of that copying. Claim 275 is also amended to clarify that the segments are reassembled in an ordered faction "to produce each chimerized but defined polynucleotide sequence encoding a full-length enzyme".

The amendments made to Claim 275 herein do not modify the nature of the subject matter claimed, but rather serve to clarify the language of the claim. Exemplary support for Claim 275 can be found throughout the specification and claims as originally filed, at least as shown in Appendix A, attached.

No new matter has been added by the present amendment. Applicants reserve the right to file a continuation or divisional application directed to any or all subject matter that may have been canceled in this application.

Interview with the Examiner

Applicants would first like to thank Examiner Lu for the courtesy of granting Applicants' representatives an interview on November 9, 2005. During the interview, the proposed amendments to the claims were discussed. In addition, the deficiencies of the Stemmer et al references, U.S. Patent No. 5,811,238 and WO 95/22625, were discussed. Specifically, the Examiner agreed that those references do not teach aligning the substrate nucleic acid sequences. The Examiner also indicated during the interview that upon allowability of the copied claim, an interference conference would be scheduled.

Objections to the specification

The Examiner objected to the specification, requiring updated information in the first paragraph of the specification, which refers to related applications. Applicants initially note that the first paragraph of the specification was indeed amended upon filing the present application, on the application transmittal form, to delete lines 6-19 at page 1, and in its place recite "This application is a continuation of and claims the benefit of U.S. Application No. 09/559,671, filed April 27, 2000, which is a continuation of U.S. Application No. 08/769,062, filed December 18, 1996 (now U.S. Patent No. 6,335,160), the disclosures of which are incorporated by reference for all purposes."

By the present Amendment, the reference to U.S. Application No. 09/559,671 has been updated to refer to "(now U.S. Patent No. 6,613,514)".

The Examiner also required amendment of the specification to refer to SEQ ID NOS on pages 83-87 and 99. This amendment has been made. As such, withdrawal of the objections to the specification is respectfully requested.

Claim objection

The Examiner objected to the claim for an alleged informality, suggesting that Applicants replace "each chimerized but defined polynucleotide sequences encoding full-length enzymes" to "each chimerized but defined polynucleotide sequence encoding full-length enzymes". Such an amendment has been made, and as such, withdrawal of this objection is respectfully requested.

Rejections under 35 USC §112, second paragraph

The Examiner rejected Claim 275 under 35 USC §112, second paragraph as being allegedly indefinite, because it is allegedly "unclear that a plurality of defined polynucleotide segments encode full-length enzymes or substrate nucleic acid sequences encode full-length enzymes." In response, step (a) is modified to clarify that it is the substrate nucleic acids which encode full-length enzymes.

The Examiner also rejected Claim 275 under 35 USC §112, second paragraph as being allegedly indefinite, because it is allegedly unclear "how the borders defining the polynucleotide segment can be selected from the aligned substrate nucleic acid sequences" and because "the aligned substrate nucleic acid sequences lack antecedent basis". In

response, "the aligned substrate nucleic acid sequences" has been clarified by reciting that the borders are selected "by aligning" the substrate nucleic acid sequences. This amendment also removes the alleged lack of antecedent basis.

The Examiner also rejected Claim 275 under 35 USC §112, second paragraph as being allegedly indefinite, because the phrase "such that said segments are reassembled in an ordered fashion for each chimerized but defined polynucleotide sequences encoding full-length enzymes" is allegedly unclear. In response, Claim 275 is also amended to clarify that the segments are reassembled in an ordered fashion "to produce each chimerized but defined polynucleotide sequence encoding a full-length enzyme".

In light of the foregoing, withdrawal of this rejection is respectfully requested.

Rejection under 35 USC §102(e)

The Examiner rejected Claim 275 as allegedly anticipated by Stemmer et al, U.S. Patent No. 5,811,238 ("the Stemmer '238 patent"). This rejection, which applies equally against the Short '449 patent from which Claim 275 is copied, is respectfully traversed.

In the discussion of the rejection, the Examiner nowhere discusses where the Stemmer '238 patent teaches that the "borders defining the polynucleotide segments are selected by aligning the substrate nucleic acid sequences", and indeed notes that the Stemmer '238 patent teaches the preparation of "random double-stranded fragments". In fact, the passages in the Stemmer '238 patent cited by the Examiner are directed specifically to the production of "random double-stranded fragments", which is the antithesis of choosing segment borders by aligning substrate sequences. Indeed, a complete review of the Stemmer '238 patent demonstrates that the Stemmer '238 patent indeed does not disclose aligning substrate nucleic

acid sequences to select the borders defining the polynucleotide segments. As such, the Stemmer '238 patent does not anticipate Claim 275. Withdrawal of this rejection is respectfully requested.

Rejection under 35 USC §103(a)

The Examiner rejected Claim 275 as allegedly unpatentable over Stemmer et al WO 95/22525 ("the Stemmer PCT"). This rejection, which applies equally against the Short '449 patent from which Claim 275 is copied, is respectfully traversed.

In the discussion of the rejection, the Examiner nowhere discusses where the Stemmer PCT teaches that the "borders defining the polynucleotide segments are selected by aligning the substrate nucleic acid sequences", and indeed notes that the Stemmer PCT teaches the preparation of "random double-stranded fragments". In fact, the passages in the Stemmer PCT cited by the Examiner are directed specifically to the production of "random double-stranded fragments", which is the antithesis of choosing segment borders by aligning substrate sequences. Indeed, a complete review of the Stemmer PCT demonstrates that the Stemmer PCT indeed neither discloses nor suggests aligning substrate nucleic acid sequences to select the borders defining the polynucleotide segments. As such, the Stemmer PCT does not render unpatentable Claim 275. Withdrawal of this rejection is respectfully requested.

Request for Interference

Applicants present this Amendment in conjunction with a Request by Applicants for Interference Pursuant to 37 C.F.R. § 41.202. Applicants present herein a proposed Count and a complete showing of the information required by 37 C.F.R. § 41.202 with regard to the

application as presently amended. The required information is set forth below under headings that correspond to the subsections of 37 C.F.R. § 41.202. In order to facilitate consideration by the Examiner, the Appendices attached hereto, which are summarized in the following table, further support the showings required under 37 C.F.R. § 41.202.

Accordingly, Applicants respectfully request that an interference be declared between the above-captioned application and the Short '449 patent.

Table of Appendices

Appendix A: Exemplary support in the present application for the pending claim of the present application.

Appendix B: A proposed Count.

Appendix C: A side-by-side comparison of Claims 1-12 of the Short '449 patent and the proposed Count.

Appendix D: A side-by-side comparison of Claim 275 of the present application, with the proposed Count.

Appendix E: A copy of the Short '449 patent

Appendix F: A copy of the present Patten '221 application.

Appendix G: A comparison of the relative filing dates for Short and Patten.

REQUEST FOR INTERFERENCE

I. IDENTIFICATION OF A PATENT THAT INCLUDES SUBJECT MATTER THAT INTERFERES WITH THIS APPLICATION

A patent that claims subject matter that interferes with subject matter claimed in the present Patten '221 application is: U.S. Patent No. 6,605,449 by Short ("the Short '449 patent") for "SYNTHETIC LIGATION REASSEMBLY IN DIRECTED EVOLUTION". The Short '449 patent issued from U.S. Application Serial No. 09/594,459, filed June 14, 2000 ("the Short '459 application"). On the face of the Short '449 patent, the 'Short '459 patent is indicated to be a continuation-in-part of Application Serial No. 09/332,835, filed on June 14, 1999 ("the Short '835 application"), now abandoned. Diversa Corporation, San Diego, California, is identified as assignee on the face of the Short '449 patent.

II. PRESENTATION OF A PROPOSED COUNT

The interfering subject matter between the Patten '221 application and the Short '449 patent relates to methods of producing libraries of chimerized enzymes. Attached Appendix B sets forth a proposed Count in chart form for the Examiner's consideration.

The proposed Count is an alternative Count, prepared after consideration of the subject matter claimed by the respective parties, which describes the interfering subject matter. The proposed Count comprises, in the alternative, Claim 6 of the Short '449 patent, or Claim 275 of the Patten '221 application. The alternative claims which comprise the count describe the same invention within the meaning of 37 C.F.R. § 41.203(a) as shown by

comparison of the claims in Appendix B, and further demonstrated by the analysis in Section III below.

III. THE PROPOSED COUNT INCLUDES DIFFERENT TERMS USED BY THE RESPECTIVE PARTIES TO DESCRIBE THE SAME INVENTION

The proposed Count is in alternative form in part because of the different language utilized by the respective parties to describe the interfering subject matter. A comparative analysis of the language used in the respective specifications is presented below.

A. "Progeny library" v. "library"

The Short '449 patent describes progeny molecules as those molecules "obtained by mutagenization of the parental set". (Col. 24, ll. 5-10) The Patten '221 application states that "starting DNA segments are recombined...to generate a diverse library of recombinant DNA segments. In general, the starting segments and the recombinant libraries generated include full-length coding sequences..." (p. 16, ll. 18-25) As such, the "progeny library" of Short and the "library" obtained by mutagenizing the starting DNA segments are the same.

B. "Predetermined polynucleotide sequence" v. "defined polynucleotide sequence"

The Short '449 patent states that "non-stochastic or non-random mutagenesis is exemplified by a situation in which a progenitor molecular template is mutated (modified or changed) to yield a progeny molecule having one or more **predetermined** mutations." (Col. 2, ll. 48-52; Emphasis added.) The Patten '221 application states that "'Coarse grain shuffling' generally involves the exchange or recombination of segments of nucleic acids, whether **defined** as functional domains, exons, restriction endonuclease fragments, or otherwise arbitrarily **defined** segments." (p. 12, l. 35 – p. 13, l. 2) As such, the

"predetermined sequences" of the Short '449 patent and the "defined sequences" of the Patten '221 application are the same, because they both relate to the knowledge of the desired mutation prior to making the mutation.

C. "Building block sequences" v. "polynucleotide segments"

The Short '449 patent states that the "building block sequences" may be single-stranded or double-stranded polynucleotides. (Col. 10, ll. 11-12) The Short '449 patent further states that "a unique overall assembly order can also be achieved... by stepping the assembly of the building blocks in a deliberately chosen sequence". (Col. 11, l. 67 – Col. 12, l. 5) Likewise, the Patten '221 application notes that "segments of nucleic acids" can be "defined as functional domains, exons, restriction endonuclease fragments, or otherwise arbitrarily defined segments." (p. 12, l. 35 – p. 13, l. 2) As such, the "building block sequences" of the Short '449 patent and the "defined sequences" of the Patten '221 application are the same, because they both relate to "arbitrarily" or "deliberately" chosen nucleic acid "chunks" which are the starting materials for making the desired end product.

D. "Non-random order" v. "ordered fashion"

The Short '449 patent states that the chimeric nucleic acid molecules are produced non-stochastically, (i.e., non-randomly) such that the "overall assembly order [that] is chosen by design" (e.g., Col. 10, ll. 32-33). Likewise, the Patten '221 application states that the gene segments are reassembled in an "ordered fashion" (p. 33, l. 12). As such, an order which is not random, is "ordered", and therefore the elements of Short Claim 6 and Patten Claim 275 are the same.

E. "Enzymes or fragments thereof" v. "full-length enzymes"

"Full-length enzymes", as recited in Claim 275 of the Patten '221 application are one member of the two-member Markush group of "enzymes or fragments thereof" recited in Claim 6 of the Short '449 patent. Applicants submit that the application of the claimed method to "fragments" of enzymes is not patentable, and as such, Applicants did not add that recitation to Claim 275. Because the "full-length" enzymes of Claim 275 of the Patten '221 application are coextensive with the "enzymes" of Claim 6 of the Short '449 patent, this element of the claims should be considered to be substantially the same, and thus, reflecting interfering subject matter between the Short '449 patent and the Patten '221 application.

F. "Sequences delineated by demarcation points selected from aligned progenitor sequences" v. "borders defining the polynucleotide segments are selected by aligning the substrate nucleic acid sequences"

The Short '449 patent discusses determining the ends of what will be "building block" sequences, by aligning a number of substrates and looking for homology therebetween:

> Thus according to one aspect of this invention, the sequences of a plurality of progenitor nucleic acid templates are aligned in order to select one or more demarcation points, which demarcation points can be located at an area of homology, and are comprised of one or more nucleotides, and which demarcation points are shared by at least two of the progenitor templates. The demarcation points can be used to delineate the boundaries of nucleic acid building blocks to be generated. Thus, the demarcation points identified and selected in the progenitor molecules serve as potential chimerization points in the assembly of the progeny molecules. (Col. 52, ll. 37-48)

Likewise, the Patten '221 application at p. 38, ll. 18-28, describes the same such process:

> In some embodiments of the invention, a search of a region of sequence space defined by a set of substrates, such as members of a gene family, having less

> than about 80%, more typically, less than about 50% homology, is desired. This region, which can be part or all of a gene or a gene is arbitrarily delineated into segments. The segment borders can be chosen randomly, based on correspondence with natural exons, based on structural considerations (loops, alpha helices, subdomains, whole domains, hydrophobic core, surface, dynamic simulations), and based on correlations with genetic mapping data.

As such, "sequences delineated by demarcation points selected from aligned progenitor sequences" and "borders defining the polynucleotide segments are selected by aligning substrate nucleic acid sequences" are the same.

G. "Non-stochastically reassembling" v. "reassembling"

If reassembly is characterized as either "stochastic" or "non-stochastic", then "non-stochastic" is one of merely two members of a Markush group. "Non-stochastically" reassembling is not a patentable distinction, because, as Short admits, "Currently available technologies in directed evolution include methods for achieving stochastic (i.e., random) mutagenesis and methods for achieving non-stochastic (non-random) mutagenesis." The Patten '221 application discloses that the design for mutagenesis can be random or non-random (see, Section F, above). As such, "non-stochastically reassembling" is not patentably distinct from "reassembling".

H. "Overall assembly order is achieved" v. "reassembled in an ordered fashion"

Achieving an overall assembly order is the same as reassembling in an ordered fashion. See Section D, above.

IV. IDENTIFICATION OF CLAIMS OF THE SHORT '449 PATENT THAT CORRESPOND TO THE PROPOSED COUNT

Claim 6 of the Short '449 patent is identical to an alternative of the Proposed Count and should be designated to correspond to the Proposed Count. Further, Claims 1-12 of the

Short '449 patent are obvious over the Proposed Count and should also be designated as corresponding to the proposed Count. A comparison of each of these claims with the Proposed Count is presented in Appendix C.

V. THE CLAIMS OF THE PATTEN '221 APPLICATION THAT CORRESPOND TO THE PROPOSED COUNT

Claims 1-15 and 274 of the Patten '221 application have been canceled. Claim 275 corresponds to the proposed count, because it is identical to an alternative of the proposed Count. Claim 275 represents a substantial copy of Claim 6 of the Short '449 patent and would be obvious over the proposed Count. Appendix D provides a side-by-side comparison of pending Claim 275 of the Patten '221 application with the proposed Count.

VI. APPLICANTS WILL PREVAIL ON PRIORITY

The present Patten '221 application was filed on August 22, 2003, and is a continuation of U.S. Application Serial No. 09/559,671, filed April 27, 2000 ("the 'Patten '671 application"), now U.S. Patent No. 6,613,514 ("the Patten '514 patent"), which is a continuation of U.S. Application Serial No. 08/769,062, filed December 18, 1996 ("the Patten '062 application"), now U.S. Patent No. 6,335,160 ("the Patten '160 patent"). Even if Short were granted the benefit of its Short '835 application, filed on June 14, 1999 (from which the Short '459 patent claims to be a continuation-in-part), Patten would still be designated Senior Party in the interference, because its '062 application was filed approximately two and a half years prior to the Short '835 application. Therefore, Patten will clearly prevail on priority.

The specifications of the Patten '221, '671, and '062 applications are essentially identical. As such, exemplary support for Claim 275 in all three applications is provided in Appendix A.

VII. A CLAIM CHART SHOWING EXEMPLARY WRITTEN DESCRIPTION OF THE ADDED CLAIMS IS ATTACHED

Exemplary support for pending Claim 275 can be found throughout the specification and claims as originally filed, at least as shown in Appendix A, attached.

VIII. CHARTS SHOWING CONSTRUCTIVE REDUCTION TO PRACTICE WITHIN THE SCOPE OF THE PROPOSED COUNT ARE ATTACHED

Appendix A, attached, shows exemplary support for Claim 275 in the present application, which is a continuation of the 'Patten '671 application, which is a continuation of the Patten '062 application. The specifications of the Patten '221, '671, and '062 applications are essentially identical. Thus, Appendix A, also serves to show constructive reduction to practice within the scope of the Count in the '221, '671 and '062 applications.

IX. CONCLUSION

Present Claim 275 is substantially copied from Claim 6 of the Short '449 patent, using the corresponding terminology of the Patten '221 application. Claim 275 was added on August 6, 2004, prior to one year after the issuance of the '449 patent on August 12, 2003. As such, Applicants' Claim 275 is not barred by 35 U.S.C. §135(b).

In view of the foregoing, Applicants respectfully request that an interference be declared employing the proposed Count set forth in attached Appendix B, with Claims 1-12

of the Short '449 patent, and Claim 275 of the present Patten '221 application being designated as corresponding to the proposed Count.

Furthermore, exemplary support in the '062 application for at least one embodiment within the scope of the proposed Count is shown in Appendix A. Since the Patten '221 application was filed December 18, 1996, well prior to the earliest Short '835 application, filed June 14, 1999, Patten should be designated as senior party. Such action is respectfully requested.

Should the Examiner feel that there are any issues outstanding after consideration of this paper, the Examiner is invited to contact Applicant's undersigned representatives to expedite prosecution. An interview regarding the present Request is requested at the Examiner's earliest convenience.

Respectfully submitted,

BINGHAM MCCUTCHEN LLP

Date November 17, 2005 By: Sharon E. Crane

R. Danny Huntington
Registration No. 27,903
Sharon E. Crane, Ph.D.
Registration No. 36,113

Bingham McCutchen LLP
Three Embarcadero Center
San Francisco, California 94111-4067
Local Telephone: (202) 778-6150
Local Facsimile: (202) 778-6155